National Institute for Health Research

NIHR Research for Patient Benefit (RfPB) Programme

Final Report Form

IMPORTANT

Final reports are required from all projects funded through the NIHR Research for Patient Benefit Programme. The RfPB Programme requires a final report in order to:

- ensure accountability
- aid in appropriate dissemination of project results
- encourage quality assurance of project outputs
- assess the impact of the research supported by the Programme
- demonstrate the achievements of the Programme

Please keep these aims in mind while completing your final report.

The report needs to offer:

a) a clear summary of the project for practitioners and users of research
b) a record of challenges faced and modifications made to the study
c) a description of experience with patient and public involvement that might help identify lessons for future research
d) an impact assessment both locally and for the NHS more broadly
e) a summary of any outputs, such as publications, from the research (which should be updated as outputs occur). Completion of this report should not pre-empt any publications that have been prepared or are in preparation detailing project results.

This form must be completed in draft prior to peer and lay review. Following review, the final version of the scientific and lay summaries will be displayed on the NIHR CCF website and will be accessible to a wide range of interested parties.

You will be required to submit a final statement of expenditure at the same time as your final report. Please note that the completed final report along with a final statement of expenditure is required prior to release of the final payment.

For further guidance or information on completion of your final report, please contact the regional Programme Manager at NIHR CCF, using the details below:

Dr Jennie Hejdenberg
Programme Manager for the London region
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NHS
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Note the maximum field sizes shown include both printing and non-printing characters such as spaces and carriage returns.

Reference Number PB-PG-0906-11154

Region London

Date submitted

For office use

1. Project Details

Project Title*:	Effect of Tailored vs Standard use of the Combined Oral Contraceptive on Continuation Rates at one year		
NHS Contracting Organisation*:	Camden Primary Care Trust		
Project Duration*: (months)	31	Grant Value:	£258,493
Start Date:	01 January 2008	Agreed Extension:	20
End Date:	31 July 2010	Revised End Date: (months)	31 March 2012

2. Grant Holder's Details

Title*:	Professor		
Surname*:	Stephenson	Forename*:	Judith
Department*:	Institute for Women's Health - Reproductive Health		
Role in Project*:	Principal Investigator		
Institution*:	University College London		
Street*:	Institute for Women's Health, 74 Huntley Street		
Town/City*:	London	County*:	London
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3. Details of the Research Team

Co-applicant 1

Title:	Dr	Surname: Wilkinson	Forename: Chris
Post held:	Lead Consultant		
Department:	Margaret Pyke Centre - Sexual & Reproductive Health Services		
Organisation:	CNWL Camden Provider Services		
Telephone:	020 3317 5488		Extension:
e-mail address:	cwilkinson@nhs.net		
Role in project:	Lead for Contraceptive Services in CPCT/Advice on all clinical aspects of study		

Co-applicant 2

Title:	Please select..	Surname:	Forename:
Post held:			
Department:			
Organisation:			
Telephone:			Extension:
e-mail address:			
Role in project:			

Co-applicant 3

Title:	Please select..	Surname:	Forename:
Post held:			
Department:			
Organisation:			
Telephone:			Extension:
e-mail address:			
Role in project:			

Co-applicant 4

Title:	Please select..	Surname:	Forename:
Post held:			
Department:			
Organisation:			
Telephone:			Extension:
e-mail address:			
Role in project:			

Co-applicant 5

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

Co-applicant 6

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

Co-applicant 7

Title: Please select.. Surname: Forename:

Post held:

Department:

Organisation:

Telephone: Extension:

e-mail address:

Role in project:

4. Changes to the Research Team

Please outline any changes that have been made to the research team, including an explanation of why these changes were required.

Heidi Chandler, Study Administrator (internal promotion) - replaced by Tina Price
Sabeena Panicker, Investigator (resigned) - work covered by Hannat Akintomide & Fiona McGregor
Hazel Quarrel, site PI Edinburgh (maternity leave) - covered by Pam Nicholson

5. Lay/Plain English Summary*

Please provide a summary of the project, including background, findings and conclusions. It is essential that you make the content of your summary and the implications of your research evident to the lay public. It should avoid technical terms and should be written in an accessible style and emphasise in particular the potential for patient benefit arising from the study.
(Maximum 2,500 characters)

Why did we do the project?
The standard way of taking the combined oral contraceptive pill (COCP or 'the pill') is to take it daily for 21 days, followed by 7 pill-free days when a monthly withdrawal bleed occurs. Women who wish to have fewer withdrawal bleeds can achieve this by simply leaving out the pill-free days, which seems to cause fewer menstrual symptoms (e.g. headache, breast tenderness, bloating) but more irregular bleeding. Another option is 'tailored' pill use, where the pill is taken daily until bleeding triggers a pill-free interval. The withdrawal bleed that occurs in the pill-free interval seems to discourage further irregular bleeding when the pill is restarted, leading to the desired combination of fewer withdrawal bleeds and less irregular bleeding. If true, tailored pill use should lead to more women staying on the pill.

What did we do?
We tested this hypothesis in a randomised controlled trial with 502 women from 8 clinics in the UK who were randomly allocated to tailored or standard use of Microgynon30, the most commonly prescribed COCP in the UK. The primary outcome was being on the COCP at one year. We found high continuation rates in both arms of the trial [80% (141/177) in the standard arm and 82% (146/179) in the tailored arm were still taking the COCP 12 months after randomisation] with no signficant difference between trial arms. Overall, 90% of women were satisfied or very satisfied with their method of contraception [94% standard arm, 86% tailored arm] and 83% with their bleeding pattern [87% standard arm v. 78% tailored arm]. The findings from in-depth interviews identified the key experiences of women taking the pill the tailored way and showed that it really suits some women, while others dislike it mainly because of not knowing when they might have bleeding with tailored pill use.

What do we conclude?
That tailored use of Microgynon30 offers a suitable alternative to standard use.

6. Keywords*

Please provide up to 8 keywords that relate to the research undertaken in this study.

Combined oral contraceptive pill

Randomised controlled trial

Continuation rates

Menstrual bleeding patterns

Tailored use of the combined oral contraceptive pill

7. Summary of Research and Findings*

Please provide a structured summary of the research including background, aims and objectives, methods, key findings, expected impact on the relevant field and conclusions.
(Maximum 10,000 characters)

Background:
High rates of unintended pregnancy and abortion in the UK are a major public health issue, with over 180,000 abortions each year. The psychological, social and economic costs of unintended pregnancy and abortion exert a heavy toll on service users and the NHS. Combined oral contraception ('the pill') is a highly effective and safe contraceptive method, but between a third and two thirds of women who do not wish to become pregnant will stop the pill after one year, and one of the chief reasons for this is irregular bleeding. Standard use entails taking the pill daily for 21 days, followed by 7 pill-free days when a monthly withdrawal bleed occurs. Many women wish to have fewer periods and the monthly withdrawal bleed with standard pill use can be prevented by simply leaving out the pill-free days. This seems to cause fewer menstrual symptoms (e.g. headache, breast tenderness, bloating) but more irregular bleeding. Another option is 'tailored' pill use, where a woman takes the pill daily until bleeding triggers a pill-free interval. The withdrawal bleed that occurs in the pill-free interval seems to discourage further irregular bleeding when the pill is restarted, leading to the desired combination of fewer withdrawal bleeds and less irregular bleeding. If true, tailored use should lead to more women staying on the pill at reduced risk of unintended pregnancy.

Aims of the trial
To compare 12 month continuation rates in women taking the combined oral contraception pill (COCP) according to a tailored regimen versus standard regimen of Microgynon 30®.

Interventions:
Standard regimen: Microgynon30 (one pill a day for 21 days, followed by a 7 day pill-free interval)
Tailored regimen: Microgynon30 taken continuously (one pill a day) with a 3 day pill-free interval (PFI) triggered by vaginal bleeding, requiring the use of sanitary protection on each day for 3 consecutive days. (Following the PFI, the COCP is takn for a minimum of 3 weeks (21 days) before another PFI to ensure contraceptive efficacy).

Study Design
A parallel randomised trial

Inclusion Criteria:
Females ≥18 and 45≤ years of age
Requesting COC as future or ongoing contraceptive method and for this to be an appropriate choice
Willing to be randomised to one of the two groups and follow protocol for 12 months
Able to give written consent
Access to the internet, has an email address and mobile phone
Willing to complete an online diary regularly, i.e. weekly, for up to 12 months after starting the allocated regimen
Exclusion Criteria:
Any recognised contraindications to COC (UKMEC criteria 3 & 4, 2007)

Primary outcome: continuation on COCP at 12 months after randomisation
Secondary outcomes:
user satisfaction with COCP regimen as contraceptive method;
user satisfaction with bleeding pattern;
adherence to tailored pill regimen;
switching to another way of taking the COCP;

switching to another method of contraception;
side effects;
pregnancy

Methods

Women were enrolled in the trial during routine clinic visits. Follow-up was by clinic visits at 3 and 9 months after randomisation to match common clinical practice, and by questionnaire at 12 months. All information was recorded electronically through a bespoke web-based electronic data capture system. Contraceptive use, bleeding patterns and user satisfaction were recorded in electronic diaries. Clinic staff were trained in use of electronic data recording as part of study protocol training before the trial started.

Sample size calculations:
A prospective study from the USA found 68% of new pill users continued with the pill at 6 months. Assuming a pill continuation rate of 50% at 12 months with conventional use, then 182 women in each arm of the trial would give 80% power at 5% significance to detect an absolute difference of 15% (or more) in continuation rates for the other arm, i.e. over 65% or less than 35% at 12 months for either of the alternative ways of taking the pill. Allowing for 25% loss to follow-up at 12 months, we aimed to recruit 250 women to each arm of the study. [If 70% of women in the standard arm continue with the pill at one year, the trial would have more than 80% power to detect a significant increase in continuation to 83% or a decrease to 55% in the other arm].

Qualitative sub-study
A qualitative sub-study was carreid out to obtain detailed, in-depth information about women's experience of the tailored regimen. A total of 15-20 interviews in each arm were planned to reach data "saturation", i.e., the point at which no new information is observed in the data. Questions used in the interview were be primarily "open-ended" and included assessment of overall satisfaction with the method as well as specific questions about bleeding, menstrual cycle-related symptoms, and sexuality (according to an Interview Topic Guide). Interviews were audio-recorded and transcribed, followed by thematic analysis (Braun and Clark 2006).

Key findings
503 women from 8 clinical sites were randomised to tailored (n=251) or standard (n=252) use of Microgynon 30® over 21 months (2/3/09 – 30/11/10)
90% of women were taking the COCP at the time of recruitment. 70% were recruited from two sites. Mean (range) age was 28 years (19-45) in both arms. There were no significant differences in marital status (73% single) or ethnic group (85% white). 96% women in each arm reported no children.

Analysis from 356 / 503 (71%) women shows that 80% of women (141/177) in the standard arm and 82% (146/179) in the tailored arm were still taking the COCP at one year [odds ratio 1.08, 95% confidence interval (0.63-1.84) adjusted for site and previous use of COCP]. However, signficantly fewer women in the tailored arm (54%) were still on their allocated regimen compared with women in the standard arm (67%) – see table. Women in the tailored arm were more likely to switch to the standard regimen - with which they were familiar – (22% versus 3%) whereas women in the standard arm were more likely to switch to another COCP formulation (9.6% versus 5.6%) which reflects usual clinical practice.

Satisfaction with regimen as a contraceptive method was high in both arms (90%), although significantly higher in the standard arm [94% in standard arm were satisfied or very satisfied with their method of contraception versus 86% tailored arm, adjusted OR 0.37 (0.17-0.79)]

Satisfaction with bleeding pattern was also high in both arms, (83%) although higher in the standard arm [87% standard arm v. 78% tailored arm, adjusted OR 0.53 (0.30-0.93)].

Among a total of 261 women (144 tailored, 117 standard) who completed electronic diaries for at least 3 consecutive months, the number of bleeding days was 36% lower in the taillored arm (790) than in the standard arm (1232) and, in the tailord arm, the average number of episodes of at least 3 days of bleeding was 1.1 [range 0-3.3] per women in 3 months.
Qualitative sub-study
In total 40 in-depth interviews were carried out by one researcher. The mean age of the women was 27 years. 18 women were in the tailored group, 14 in the standard group and 8 were 'switchers' 9from tailored to standard). The main themes identifed were
Ease of tailored regime; Changes in physical symptoms (e.g., bloating, breast tenderness); Adjustment to reduced, or absent, bleeding; and Unpredictability about when bleeding would occur. Several women reported very positive experiences with tailored use of the pill, others did not like the "unpredictability" of not knowing when they would bleed and a few had increased anxiety about possible pregnancy.

Examples of experience of bleeding patterns from the in-depth interviews:

"The thing I found most noticeable and interesting was the adjustment to not bleeding monthly which I initially found – not unpleasant – but something to get used to and I felt like I'd lost a bit of a routine, like there was something missing…"

"…not bleeding every month…I found that to be an enormous improvement to just general quality of life. Because I used to get – even on the pill – quite dramatic shifts in mood and appetite" [Tailored]

"…because initially I thought 'would I feel less of a woman for not bleeding every month and I found that a little bit unsettling but I have to say that the reduction of inconvenience of not having a month bleed is a real benefit" [Tailored]

" I was really worried about the uncertainty of whenI would have a bleed, and it started to stress me out a bit, and so I just really got to the stage where I thought I would be much more comfortable on the standard week" [Switcher]

Expected impact
The Faculty of Sexual and Reproductive Heatlh care has recently published guidance on tailored COCP regimens, but there are no data from UK trials. Apart from one trial of tricyling in USA, this is the largest RCT of a tailored COCP regimen. It fills some important gaps in evidence about the effects of extended COCP regimens. Most previous studies have assessed attitudes towards extended use of the pill, or amenorrhea, rather than women's actual experience. Our findings from the qualitative substudy contribute to the literature by providing detailed data about women's experiences with tailored use of the COC

Conclusions
We found high continuation rates on the COCP at one year, with no significant difference between women randomised to standard use or tailored use. Satisfaction rates with method and bleeding pattern at one year are also high in both groups, although statistically signficant differences favoured the standard group. Qualitative data showed that the tailored regimen suits some women much better than the standard regimen. The main concerns were about the unpredictablilty of when they would bleed and less often, anxiety about possible pregnancy. Overall our findings suggest that tailored use of Microgynon30 offers a suitable alternative to standard COCP use.

8. Changes in the project since initial approval*

Please summarise any changes made to the project as outlined in the original proposal and outline the reasons for these changes. If there were no changes to the original plans write 'not applicable'. **(Maximum 2,500 characters)**

Aims and objectives:
There were no changes to the aims of objectives. There were several amendments e.g. change of local PI at study sites that were approved by the REC; these are listed in an attachment.

Research Plan and Methodology:
The only change to the research plan and methodology was to devise an alternative shorter outcome questionnaire that was sent to women who had not completed the original (longer) outcome questionnaire at 12 months. This enabled us to increase the follow-up rate for the primary and key secondary outcomes from 40% to 71%.

9. Patient and Public Involvement*

The RfPB Programme is particularly keen to learn from the experiences of research teams regarding patient and public involvement (PPI). Please provide comment on your experiences with PPI, any changes made and lessons drawn. Please include detail of PPI with dissemination and with trajectory into practice both in the project and beyond. **(Maximum 5,000 characters)**

After the start of the trial we established a Research and Innovation Forum (user group) at the Margaret Pyke Centre to gain input from service users and potential users to improve the quality and impact of research studies as well as informing service developments. We were therefore able to ask for guidance from the Forum about dissemination strategy and next steps. Participants in the tailored pill trial were among the first members of the Forum because they indicated that they were willing to be involved in further research and have remained active members of the Forum since the end of the trial. This month (May 2012) we presented the findings of the trial to the Forum and received helpful feedback about next steps, and in particular what kind of study we might do to build on these findings.

10. Next Steps to Patient Benefit*

Please provide comment on the likely implications for practice which may result from the outcomes of this project and the next steps to be taken to ensure patient benefit both locally and more broadly. Steps already taken and planned for the future should be included. While in funding research, RfPB emphasises a 3-5 year trajectory into practice, it is important not to 'overclaim' and care should be taken to cover the limitations of the study and any risks associated with implementation. Where the project is a pilot, include details of plans for a definitive study, including the likely funder and timetable for its submission. Please give reasons if there is no plan to go forward to a trial at this stage. **(Maximum 5,000 characters)**

The trial findings provide important information about a form of extended (tailored) use of the COCP which are expected to lead to increased choice and uptake of this regimen over the next 2-5 years. When the trial started, there was no clinical guidance from the Faculty of Sexual and Reproductive Healthcare on this topic. In October 2011, guidelines from the Faculty were published based on data from outside the UK that generally supported use of extended / tailored regimens. However, none of the studies was conducted in the UK. This trial is the only trial of extended / tailored pill use in the UK and the second largest trial in the published literature. It also provides data on tailored use of the most widely prescribed COCP in the UK, Microgynon30. The likely implications are that the Faculty guidelines, scheduled for review in 2016, will be more evidence based using our trial data. Feedback from clinicians, including some who did not take part in the trial, is that the data will enable them to advise women 1) that there is good evidence to support use of a tailored regimen and 2) to provide robust information about what women can expect in terms of bleeding and other experience, if they choose a tailored COCP regimen.

Based on the trial findings and the feedback from the patient Forum (see section 9) there are two possible further studies that we would conduct. 1) In a population where extended / tailored regimens are not generally discussed with patients, a randomised trial of standard counselling about the taking the COCP ('pill teach') versus extended counselling to include the tailored regimen could be conducted, again with COCP continuation rates as the primary outcome. The research question is " if women are advised about a range of ways of taking the pill, rather than just the standard way, are they more likely to find a regimen that suits them and therefore more likely to stay on the pill?"

2) In other settings, some clinicians are already advising some women about extended use of the COCP. In these settings an RCT of standard versus extended COCP counselling is unlikely to be feasible. However, a qualitative study involving developing (with user input) a standardised approach to counselling women, followed by exit interviews with patients to find out whether they understood the advice and what decision (if any) they had made, followed by short-term follow-up to find out what COCP regimen (if any) they were on, would be the most useful next step to improving evidence based practice in contraceptive services.

11. Key Presentations and Publications*

Please list here any presentations and publications which have resulted from the work. This should include journal articles, conference proceedings, press releases and all publications in the lay and scientific press, including website links to published articles if appropriate. Items that are forthcoming should also be included. **Please note you are contractually obliged to provide 28 days notification prior to any publication.**

Author (s)	Title	Reference/Further Details
Panicker S, Shawe JA, Akintomide H, Wilkinson CL, Stephenson JM	Effect of tailored vs standard use of the combined oral contraceptive pill on continuation rates at one year	Poster Presentation at the Institute for Women's Health International Conference, 9th - 11th November 2009
Panicker S, Shawe JA, Akintomide H, Wilkinson CL, Stephenson JM	Effect of tailored vs standard use of the combined oral contraceptive pill on continuation rates at one year	Abstract submitted to the European Society of Contraception and Reproductive Health's 11th Congress (19th - 22nd May 2010)
Graham CA,Panicker S, Stephenson JM	Women's Experiences with Tailored Use of a Combined Oral Contraceptive: A Qualitative Sub-Study	Poster Presentation at the UCL Institute for Women's Health Annual Conference, 12th May 2011
Stephenson JM,Shawe JA, Panicker S, Akintomide H, MacGregor F, Sauer U, Wilkinson C, Brechin S, Masters T, Gunn C, MacAllister K, Kubba A, O'Brien PA, Webb A, Brima N, Chandler H, Price T	Effect of tailored versus standard use of the combined oral contraceptive pill on continuation rates at one year	Abstract submitted to the faculty of Sexual & Reproductive Health Annual Scientific Meeting, 24th-25th April 2012
McGregor F, Shawe JA, Panicker S, Akintomide A, Sauer U, Wilkinson C, Brima N, Copas A, Stephenson JM & Tailored Pill Study Group	Effect of Tailored versus Standard Use of the Combined Oral Contraceptive Pill on Continuation Rates at One Year	Prize winning Poster Presentation at the UCL Institute for Women's Health Annual Conference, 21st May 2012
Stephenson JM,Shawe JA, Panicker S, Akintomide H, MacGregor F, Sauer U, Wilkinson C, Brechin S, Masters T, Gunn C, MacAllister K, Kubba A, O'Brien PA, Webb A, Brima N, Chandler H, Price T	Effect of tailored versus standard use of the combined oral contraceptive pill on continuation rates at one year	Abstract submitted to European Society of Contraception & Reproductive Health, 20th - 23rd June 2012
Panicker S, Mann S and Stephenson JM	Extended Use of COCP: How has it evolved	Article submitted to Contraception